Stereospecific Synthesis of P-Epimeric (S_P,S_P)-Bis-[(−)-menthyloxy(phenyl)-thiophosphoryl] Disulphide. An Unusual Case of Steric Selection

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Iodine–water oxidation of compound **1**, condensation of **1** with $(R)_p$-**7** together with the reaction of the latter with trimethylsilyl azide results in the formation of stable $(S)_p(S)_p$-**2**.

In an earlier paper we reported the synthesis of $(R)_P$ and $(S)_P$ compounds R(R′O)P(S)SCl **3** (R = L-menthoxy, R′ = ethyl).[1] These compounds are closely related to the disulphides $[R(R'O)P(S)S]_2$ **2**. Both types of compounds have a strongly electrophilic sulphur atom attached to a good leaving group which gives them properties similar to pseudohalogen species.[2]

Recently, we have found an unusual case of stereoselectivity leading to the pure disulphide **2** having $(S)_P$ configuration on both phosphorus atoms. This disulphide was prepared in three ways presented in Schemes 1 and 2.

Compound **1** was prepared from dichlorophenylphosphine $PhPCl_2$ in three steps as shown in Scheme 1. The intermediate compound **4** was not isolated.

Oxidation of the salt **1** gave the pure disulphide $(S)_p(S)_p$-**2** in almost quantitative yield. A sharp melting point and a single signal observed by ^{31}P NMR spectroscopy were indicative of high purity of the disulphide **2**, which was thought likely to have the same configuration at both phosphorus atoms. These observations corroborate the X-ray analysis data. The absolute configuration at both phosphorus atoms has been established to be $(S)_P$ (Fig. 1). The *X*-ray structure analysis† showed that **2** has a twofold crystallographic symmetry axis lying on the S–S sulphide bond. The menthyl configuration is that of L(−)-menthol[3] and additionally the configuration of this group has been used as an internal test of the correctness of the configuration determination.

Similarly the stoichiometric reaction of $(R)_p$-**7** with trimethylsilyl azide afforded the disulphide $(S)_p(S)_p$-**2** in almost quantitative yield (Scheme 2).[4] The analogous reaction is known for simple sulphenyl and selenyl systems.[5]

The next objective was an attempt to generate disulphide **2** containing two different P-chiral centres. Our strategy was to couple the dithioacid **1** with $(R)_p$-**7**. Scheme 2 represents the synthesis of $(R)_p$-**7** and its condensation with the salt **1**. The key intermediate $(S)_p$-**5** was obtained by recrystallization from an equimolar mixture of $(S)_p$ and $(R)_p$ isomers. The diastereoisomer $(R)_p$-**5** undergoes epimerisation either thermally or under the influence of acids. Therefore, almost the whole mixture was converted into the isomer $(S)_p$-**5**. By treating $(S)_p$-**5** with morpholidosulphenyl chloride, $(R)_p$-**6**[6] was produced stereospecifically. It was further transformed into the

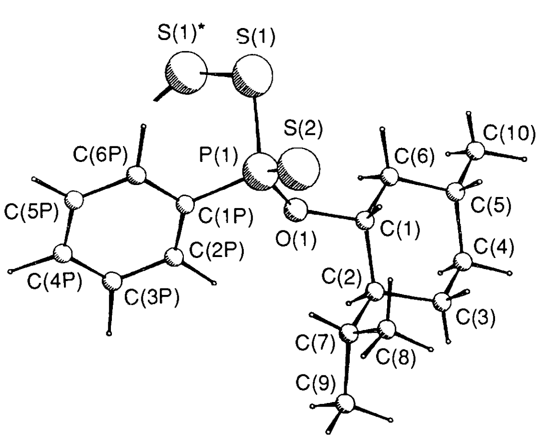
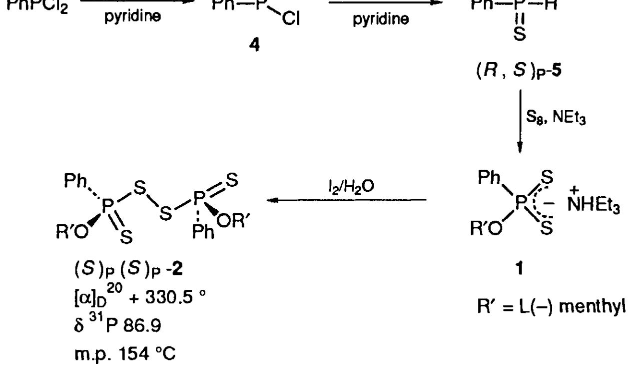


Fig. 1 View of the symmetrically independent half of the molecule with the atom numbering scheme. The asterisk indicates atoms related by the twofold symmetry axis (symmetry operation $-x,-y,z$). Important distances (Å) and torsion angles (°) involving the P(1) atom: P(1)–S(1) 2.101(2), P(1)–S(2) 1.926(2), P(1)–O(1) 1.573(2), P(1)–C(1P) 1.808(5); S(1)*–S(1)–P(1)–S(2) −159.6(1), P(1)–S(1)*–P(1)* −113.7(1), S(1)*–S(1)–P(1)–O(1) 73.7(1), S(1)–P(1)–O(1)–C(1) 91.0(3).



Scheme 1

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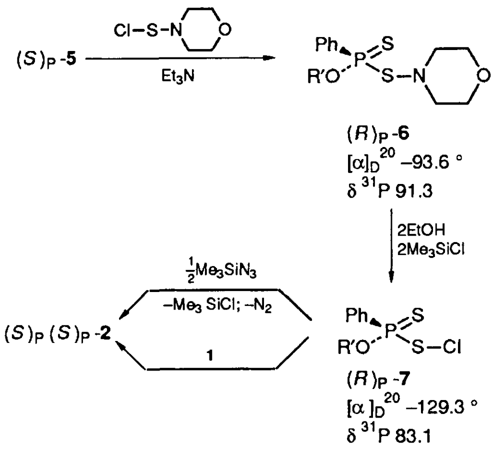
† *Crystal data* for $C_{32}H_{48}O_2P_2S_4$: M_w = 654.94, orthorhombic, space group $P2_12_12$, a = 17.083(3), b = 10.952(2), c = 9.586(2) Å, V = 1793.6(5) Å^3, Z = 2, D_c = 1.21 g cm^{-3}, $F(000)$ = 700, Cu-Kα (λ = 1.54178 Å), μ = 33.36 cm^{-1}. Single crystals grown from an n-hexane solution; crystal size 0.61 × 0.36 × 0.17 mm, unit cell dimensions by least-squares method from 15 reflections centred on a Syntex P2$_1$ diffractometer. Of 2690 reflections measured by θ-2θ scan technique (2θ range 0–116°; index range h −18 to 18, k 0 to 11, l 0 to 10), 2581 were unique, and 2438 observed ($F_o/\sigma > 2$). The P, S and O atoms were found by direct methods, the remaining non-H atoms were located in a Fourier map. Positions of 17 H-atoms were determined from the difference map and the C(8) and C(9) methyl H-atoms placed in calculated positions. The parameters for H-atoms were kept fixed throughout the refinement. The refinement, using atomic scattering factors[8] with the imaginary dispersion term $\Delta f'' = 0$ for all non-H atoms, converged at $R(R_w)$ 0.0433(0.0519). Atomic parameters from this refinement were used in the determination of absolute configuration. Two sets of structure factors applying anomalous-dispersion factors were calculated;[9] one set with positive $\Delta f''$ and the second with negative $\Delta f''$. Resulting factors were: $R(+)$ = 0.0406, $R_w(+)$ = 0.0495 and R(−) = 0.0490, $R_w(-)$ = 0.0583 for 181 parameters and 2438 reflections. Application of Hamilton's R-factor ratio test[10] gave theoretical $\mathscr{R}_{1,2257,0.005}$ = 1.00176 while value obtained for this structure was $\mathscr{R} = R_w(-)/R_w(+)$ = 1.1777. Hence, because $\mathscr{R} > \mathscr{R}_{1,2257,0.005}$, the probability that the opposite enantiomer is correct can be rejected at the 99.5% confidence level. Final least-squares refinement of the correction enantiomer gave R = 0.0406 and R_w = 0.0493 [$w = 1/\sigma^2(F_o)$]. Δ/σ_{max} in last cycle of refinement 0.002; final $\Delta\rho_{max}$ 0.32 eÅ^3 near P atom. Calculations were carried out using the SHELX76 system.[11] Final atomic coordinates (for the correct enantiomer), bond lengths and angles, and thermal parameters have deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.



Scheme 2

pure sulphenyl chloride $(R)_P$-**7** by treatment with hydrogen chloride produced *in situ* from trimethylsilyl chloride and ethanol.[1,7] Surprisingly the condensation of $(R)_P$-**7** with the salt **1** also afforded the disulphide $(S)_P(S)_P$-**2** as the major product identical with those prepared by the oxidation of **1** and the reaction of the sulphenylchloride $(R)_P$-**7** with trimethylsilyl azide. No other diastereoisomers $(R)_P(R)_P$-**2** and $(R)_P(S)_P$-**2** could be detected by ^{31}P NMR spectroscopy. It is important to mention that according to ^{31}P NMR spectroscopy exclusive formation of the disulphide $(S)_P(S)_P$-**2** takes place prior to its appearance as a crystalline species.

At present we have no rational explanation of the stereochemical selection observed. Similar reactions of the analogous model containing ethoxy group instead of phenyl do not show similar stereochemical selectivity. The aromatic ligand attached to the phosphorus atom may be important in this case.

The present results describe the first access to pure diastereoisomeric disulphides of the type **2**, which is used as an intermediate in synthesis of P-chiral derivatives of phosphorus dithioacids. Many other examples of enantioselective reactions have been discussed recently by Noyori and Kitamura.[12]

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